The Magic Bullet for Prevention of CVD and Cancer?

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Learning objectives

1. List the benefits and harms of using aspirin to prevent CVD and cancer.
2. Summarize the evidence-based recommendations for prescribing aspirin in primary and secondary prevention of CVD.
3. Describe available aspirin preparations and their clinical application in patients with CVD and other co-morbid conditions and harms of using aspirin to prevent CVD and cancer.

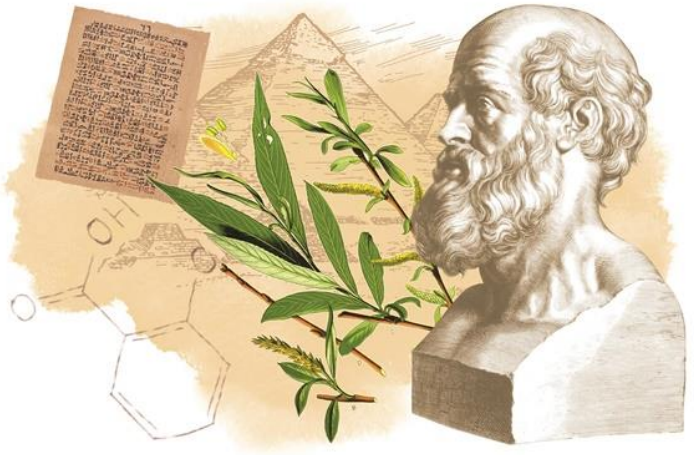
Outline

- History of aspirin
- Benefits and harms
- Guidelines
  - CVD secondary prevention
  - Primary prevention of CVD and CRC
- Future directions

Aspirin

Aspirin, also known as acetylsalicylic acid (ASA), is a medication used to treat pain, fever, or inflammation. Specific inflammatory conditions which aspirin is used to treat include Kawasaki disease, pericarditis, and rheumatic fever.

History of aspirin



- **c3000 – 1500 BC:** Willow is used as a medicine by ancient civilisations like the Sumerians and Egyptians. The Ebers papyrus, an ancient Egyptian medical text, refers to willow as an anti-inflammatory or pain reliever for non-specific aches and pains.
- **400 BC** In Greece Hippocrates gives women willow leaf tea to relieve the pain of childbirth.
- **1763** Reverend Edward Stone of Chipping Norton near Oxford gives dried willow bark to 50 parishioners suffering rheumatic fever.
- **1828** Joseph Buchner, professor of pharmacy at Munich University, Germany, succeeds in extracting the active ingredient from willow, producing bitter tasting yellow crystals that he names salicin.
- **1897** German chemist Felix Hoffmann, possibly under the direction of colleague Arthur Eichengrün, finds that adding an acetyl group to salicylic acid reduces its irritant properties and Bayer patents the process.
- **1899** Acetylsalicyclic acid is named Aspirin by Bayer. The letter 'A' stands for acetyl, "spir" is derived from the plant known as Spiraea ulmaria (meadowsweet), which yields salicin, and "in" was a common suffix used for drugs at the time of the first stable synthesis of acetylsalicylic acid.

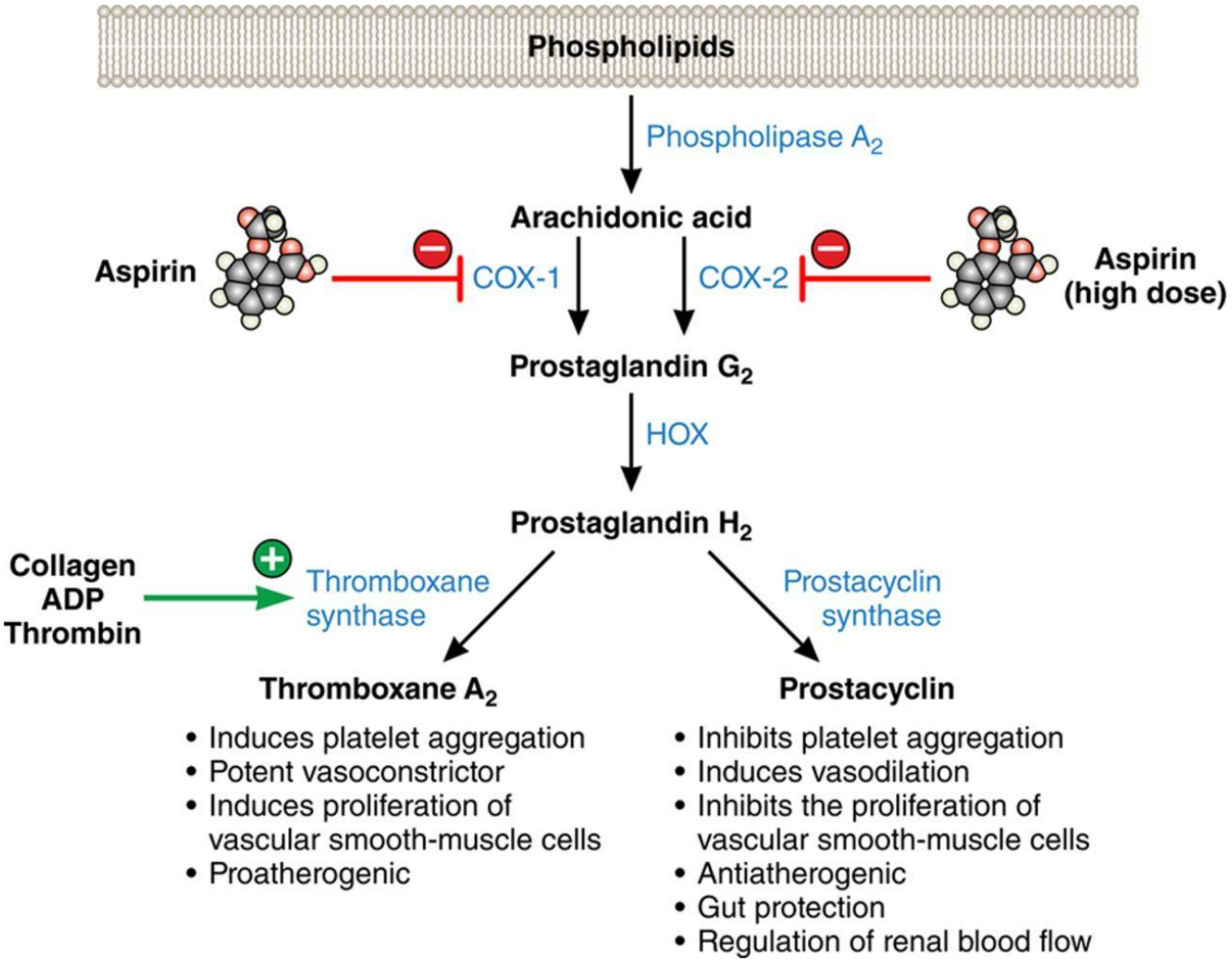
History of aspirin, cont.

- **1971:** John Vane, professor of pharmacology at the University of London, publishes research describing aspirin's mechanism of action (dose-dependent inhibition of prostaglandin synthesis) (*Nature New Biology* 1971;231:232).
- **1974** Data from the first randomized controlled trial of aspirin in the secondary prevention of death from heart attack show a reduction in total mortality of 12% at 6 months and 25% at 12 months but the results are statistically inconclusive (BMJ 1974;1:436).
- **1982** Sir John Vane, Sune Bergström and Bengt Samuelsson win Nobel prize for discovering the role of aspirin in inhibiting prostaglandin production.
- **~1990** Results from the CPS (cancer prevention study)-II, a large US prospective cohort study, confirm the cancer benefits of aspirin seen in smaller observational studies (*NEJM* 1991;325:1593 and *Cancer Research*1993;53:1322).
- **2009:** A meta-analysis by the ATT (antithrombotic trialists) collaboration suggests that aspirin has substantial overall benefit in secondary prevention but in primary prevention, aspirin is of uncertain net value as the reduction in occlusive events needs to be weighed against any increase in major bleeds (*Lancet* 2009;373:1849).

Potential benefits of long-term aspirin use

- Cardiovascular diseases

Mechanisms of action in CVD prevention

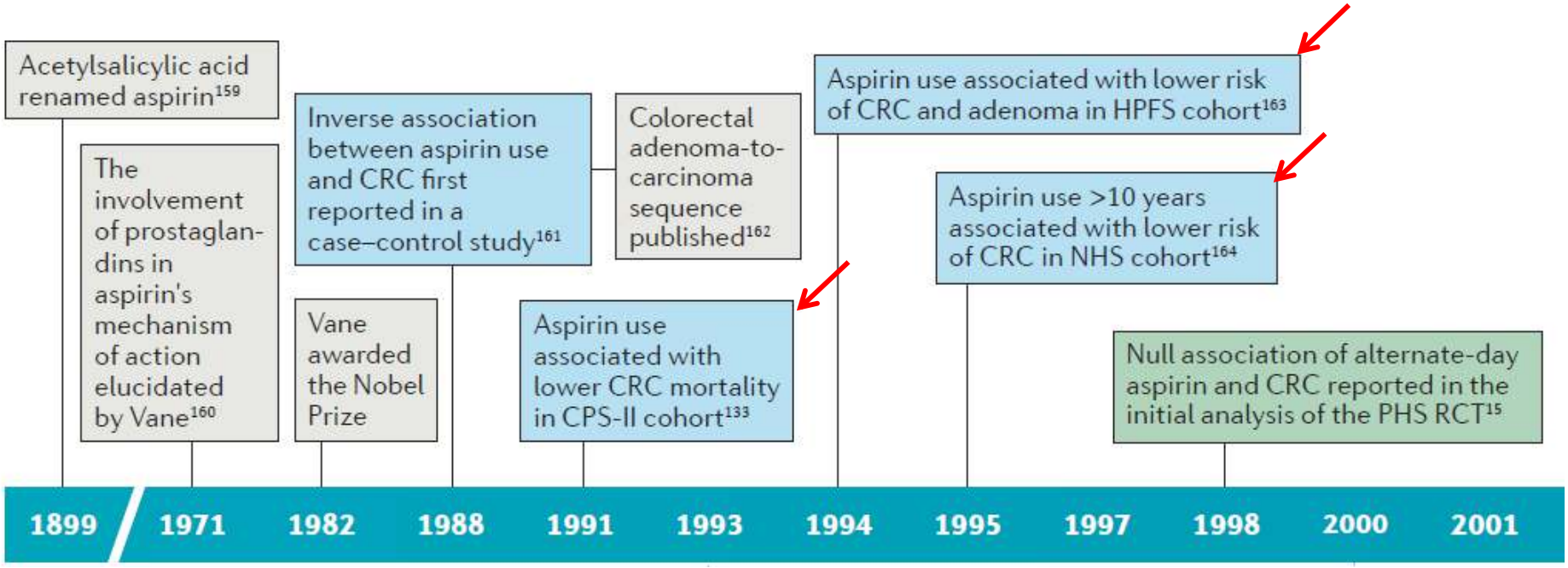


Capadanno et al, Circulation 2016

Potential benefits of long-term aspirin use

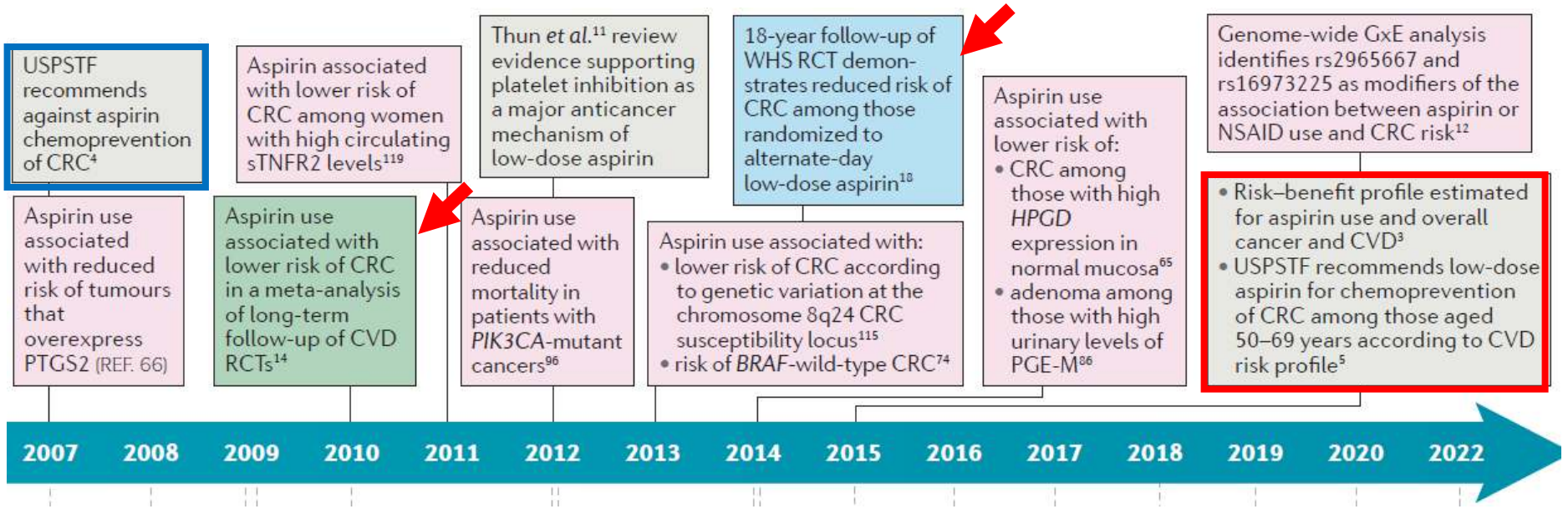
- Cardiovascular diseases
- Colorectal cancer

Milestones & notable findings on aspirin and risk of colorectal neoplasia



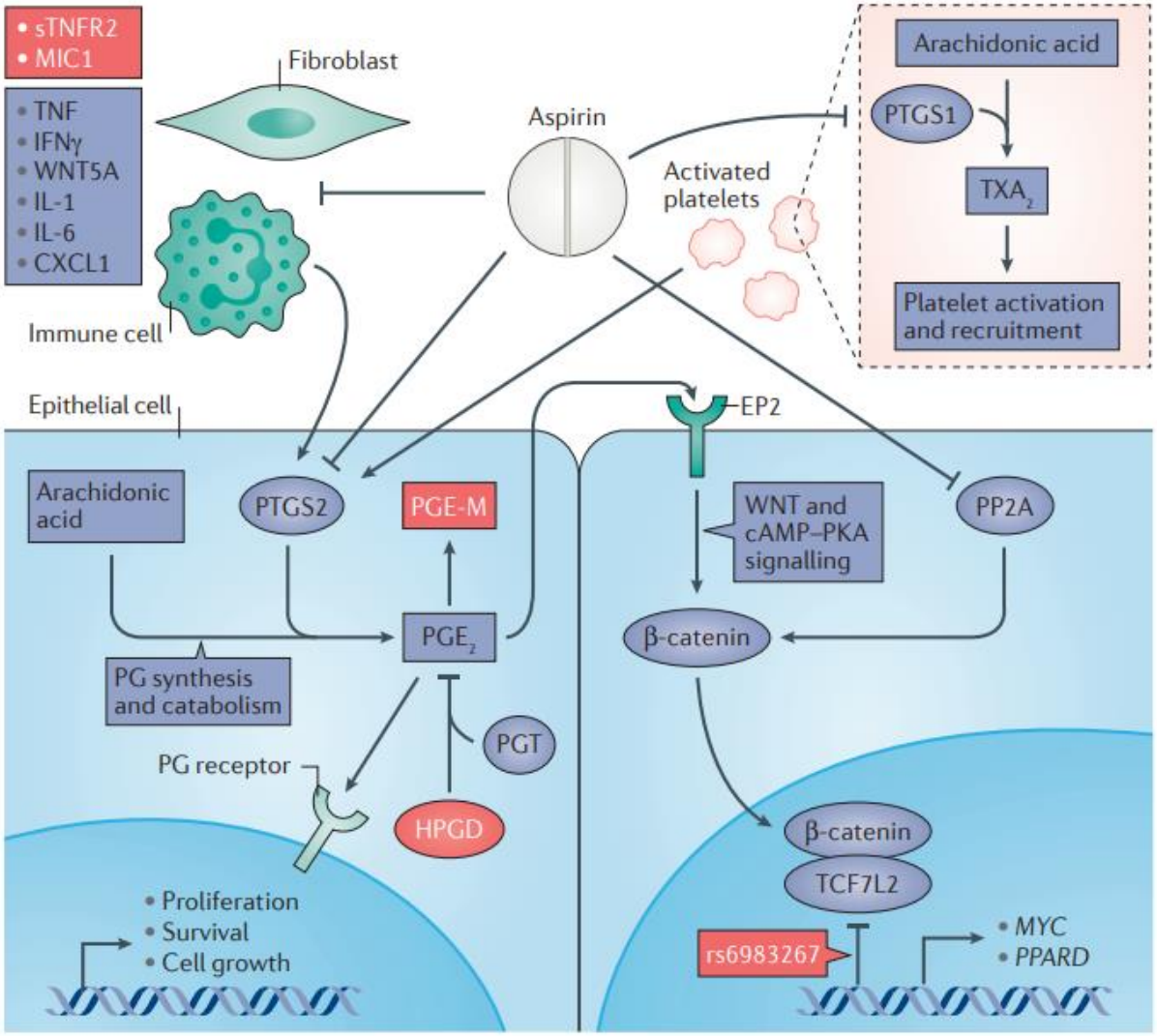
Drew DA, Cao Y and Chan AT, Nat Rev Cancer 2016

Milestones & notable findings on aspirin and risk of colorectal neoplasia



Drew DA, Cao Y, and Chan AT, Nat Rev Cancer 2016

Mechanisms for aspirin's chemopreventative effects



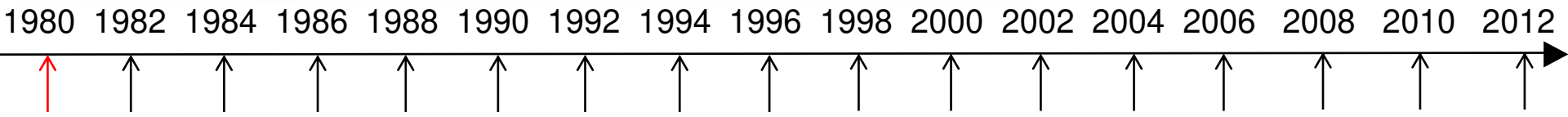
Drew DA, Cao Y and Chan AT, Nat Rev Cancer 2016

Potential benefits of long-term aspirin use

- Cardiovascular diseases
- Colorectal cancer
- Emerging
  - Reduce risk of other cancers, particularly GI tract

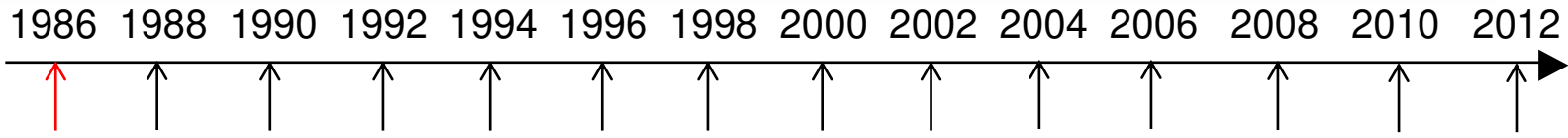
Study population

Nurses' Health Study (n=121,700)



Diet
Aspirin
BMI
Med. Hist.
Tobacco

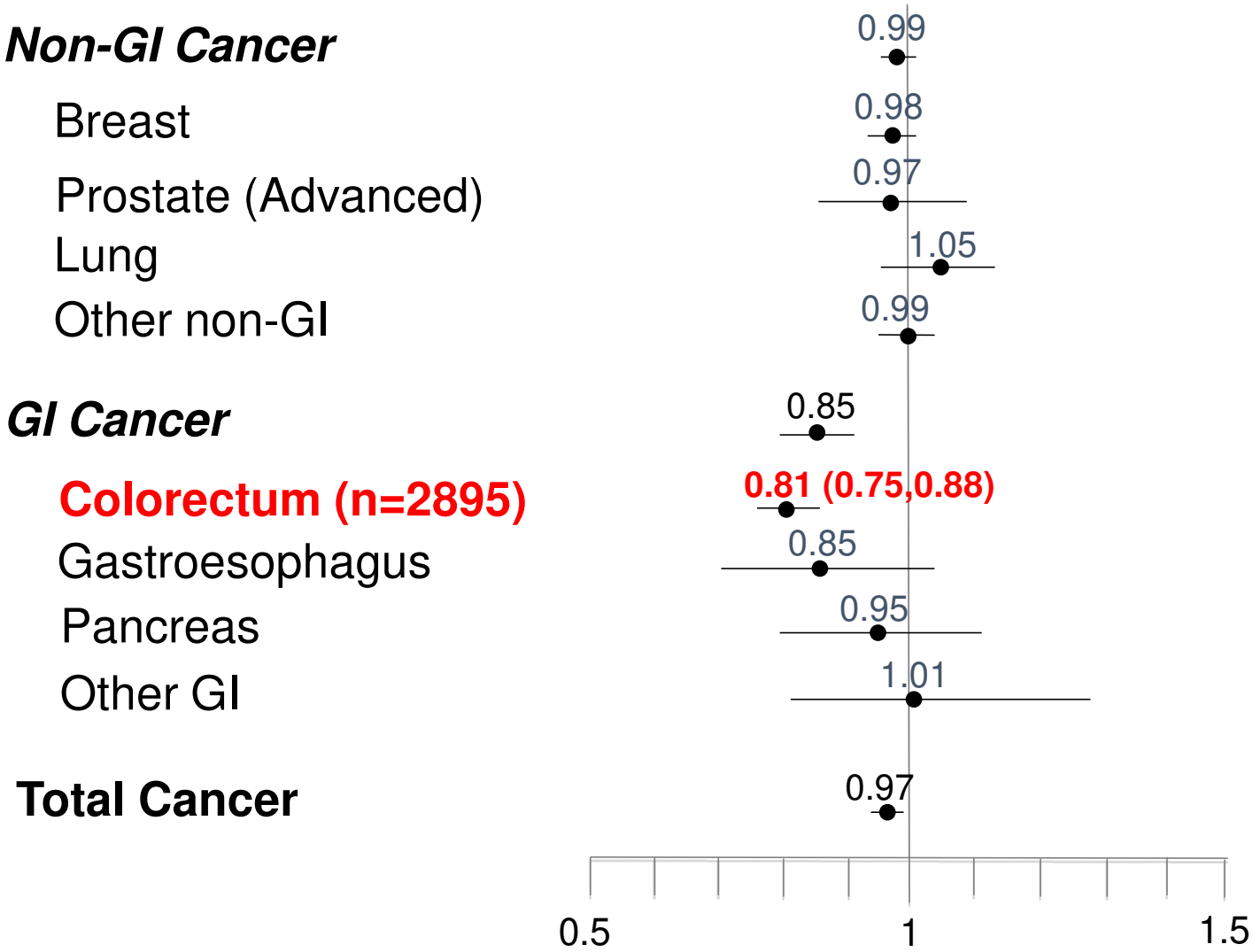
Health Professionals Follow-up Study (n=51,539)



Diet
Aspirin
BMI
Med. Hist.
Tobacco

Aspirin reduces risk of GI cancers

NHS 1980-2012 HPFS 1986-2010



Cao *et al*, JAMA Oncology 2016

Aspirin may reduce risk of other cancers: Review of observational studies and RCTs

Table 3: Risk ratios for incidence and mortality of different events due to aspirin use; used in benefit-harm calculations.

Event	Incidence		Mortality	
	Best estimate	Conservative	Best estimate	Conservative
Colorectal cancer	**0.65**	0.70	**0.60**	0.65
Oesophageal cancer	**0.70**	0.75	**0.50**	0.55
Gastric cancer	**0.70**	0.75	**0.65**	0.70
Lung cancer	**0.95**	1.00	**0.85**	0.90
Prostate cancer	**0.90**	0.95	**0.85**	0.90
Breast cancer	**0.90**	0.95	**0.95**	1.00

Cuzick et al, Annals of Oncology 2015

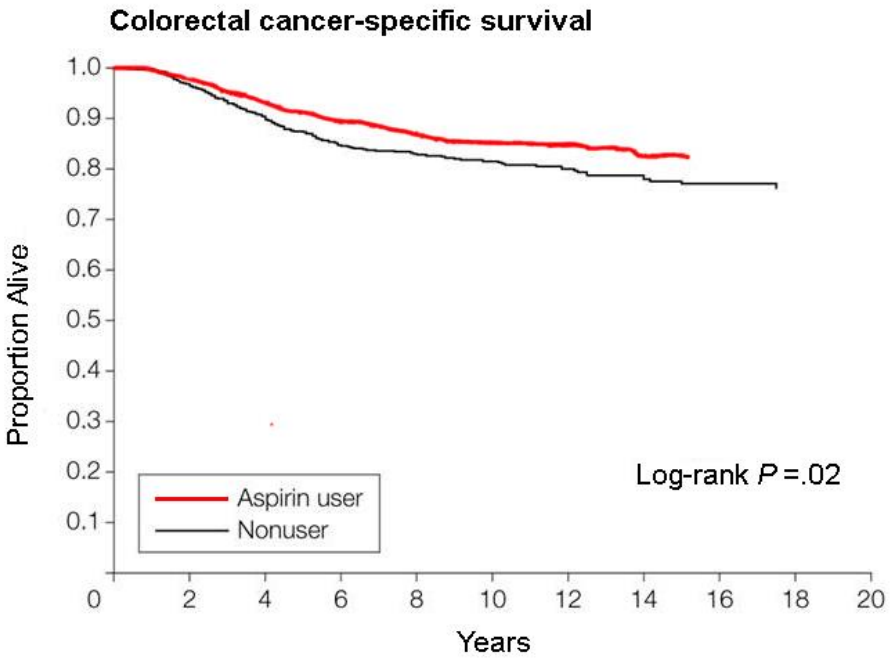
Potential benefits of long-term aspirin use

- Cardiovascular diseases
- Colorectal cancer
- Emerging
  - Reduce risk of other cancers, particularly GI tract
  - Reduce metastasis after cancer diagnosis

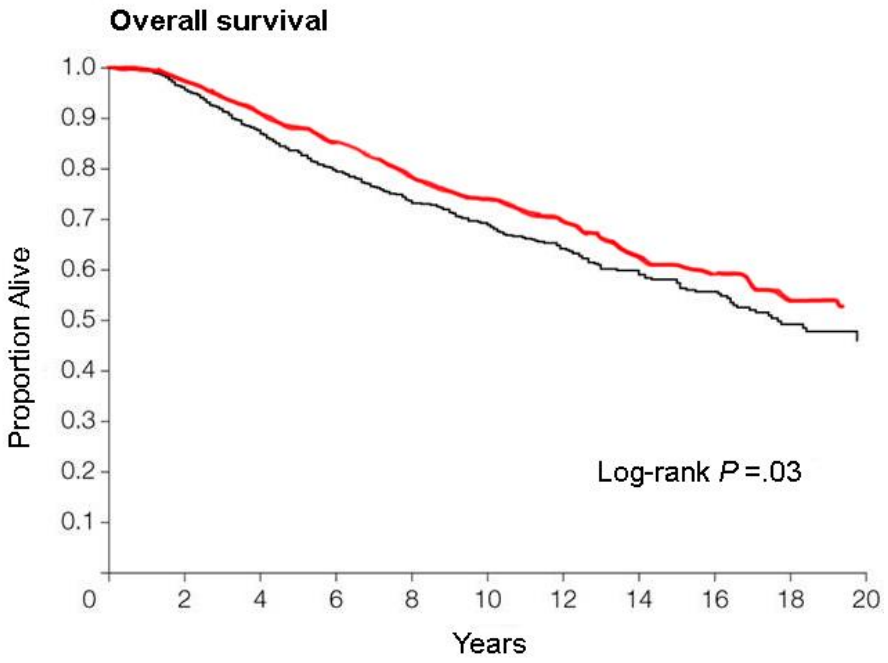
Aspirin use and CRC patient survival

NHS 1980-2008 HPFS 1986-2008

HR: 0.71 (95% CI 0.53-0.95)



HR 0.79 (95% CI, 0.65-0.97)



Chan et al, JAMA 2009

Daily aspirin on risk of cancer metastasis: a study of incident cancers during RCT

	Cancers/person-years		HR (95% CI)	p value
	Aspirin	Control		
All solid cancers*				
Any metastasis	182/60 560	211/47 703	0·73 (0·60–0·89)	0·002
Definite distant metastasis	92/60 656	118/47 830	0·64 (0·48–0·84)	0·001
Metastasis with site unspecified	90/60 621	93/47 836	0·85 (0·63–1·14)	0·27
Metastasis at initial diagnosis	131/60 666	140/47 891	0·79 (0·62–1·01)	0·06
Metastasis on follow-up	51/60 611	71/47 775	0·60 (0·42–0·86)	0·006
Local disease only	227/60 079	155/47 477	1·24 (1·01–1·53)	0·040
Metastasis status unknown	101/60 604	111/47 855	0·77 (0·58–1·01)	0·056

Rothwell et al, Lancet 2012

ADD Aspirin: RCT of daily 100/300mg among 11,000 patients with 4 types of early stage cancer (Endpoint: disease-free/overall survival)

Breast

We aim to recruit 3100 individuals who have had surgery to remove an early stage breast cancer.

CURRENT STATUS:
OPEN

Detailed eligibility criteria available here

Top recruiters: Worcestershire Royal Hospital, Tata Memorial Hospital Mumbai, Western General Hospital, Churchill Hospital Oxford

PARTICIPANTS REGISTERED: 2940
PARTICIPANTS RANDOMISED: 2408

Colon/Rectum

We aim to to recruit 2600 individuals who have had surgery to remove an early stage bowel cancer.

CURRENT STATUS:
OPEN

Detailed eligibility criteria available here

Top recruiters: Bristol Haematology & Oncology Centre, St James 's University Hospital, Velindre Hospital, Western General Hospital

PARTICIPANTS REGISTERED: 1734
PARTICIPANTS RANDOMISED: 1401

Gastro

We aim to recruit 2100 individuals who have had surgery or a combination of chemotherapy and radiotherapy to treat a cancer of the stomach or oesophagus (food pipe).

CURRENT STATUS:
OPEN

Detailed eligibility criteria available here

Top recruiters:
Tata Memorial Hospital Mumbai, Christie Hospital, UHCW, Manor Hospital, Churchill Hospita, Oxford

PARTICIPANTS REGISTERED: 327
PARTICIPANTS RANDOMISED: 259

Prostate

We aim to recruit 2120 individuals who have had surgery or radiotherapy to treat an early stage prostate cancer.

CURRENT STATUS:
OPEN

Detailed eligibility criteria available here

Top recruiters: UCHW, Darent Valley Hospital, Queen Elizabeth Hospital King's Lynn, University Hospital of Wales

PARTICIPANTS REGISTERED: 1400
PARTICIPANTS RANDOMISED: 1168

Coyle, Contemp Clin Trials, 2016

Summary 1
Potential benefits of long-term aspirin use

- Cardiovascular diseases
- Colorectal cancer
- Emerging
  - Reduce risk of other cancers, particularly GI tract
  - Reduce metastasis after cancer diagnosis

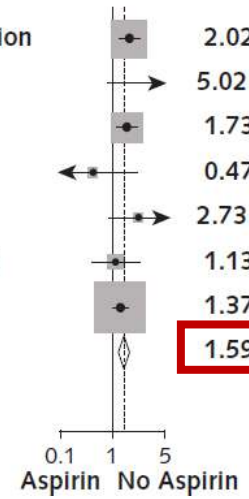
Harms of aspirin use

- Gastrointestinal bleeding
- Hemorrhagic stroke

Risk of major GI bleeding in CVD primary prevention RCTs

Meta-analyses for USPSTF 2016

Study, Year (Reference)	Time Point, *y*	Dose, *mg/d*	Population	OR (95% CI)	Events, *n/N*	
					Aspirin	No Aspirin
HOT, 1998 (24)	3.8	75	Men and women with hypertension	2.02 (1.40–2.93)	77/9399	37/9391
IPAD, 2008 (25)	4.4	81 or 100	Men and women with diabetes	5.02 (0.87–29.05)	4.5/1263	0.5/1278
PHS, 1989 (26)	5	162.5	Male physicians	1.73 (1.10–2.70)	49/11 037	28/11 034
BMD, 1988 (27)	6	500	Male physicians	0.47 (0.09–2.57)	3/3429	3/1710
TPT, 1998 (29)	6.8	75	Men at high risk for IHD	2.73 (0.68–10.95)	6/1268	2/1272
AAA, 2010 (30)	8.2	100	Men and women with ABI ≤0.95	1.13 (0.43–2.92)	9/1675	8/1675
WHS, 2005 (32)	10.1	50	Female health professionals	1.37 (1.05–1.78)	129/19 934	94/19 942
Overall: $I^2 = 22.2\%$; $P = 0.260$				1.59 (1.32–1.91)	277.5/48 005	172.5/46 302

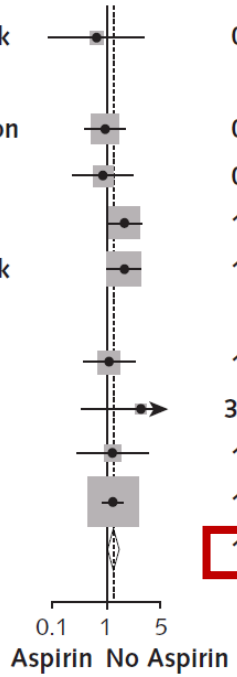


Whitlock et al, Annals of Internal Medicine, 2016

Risk of hemorrhagic stroke in CVD primary prevention RCTs

Meta-analyses for USPSTF 2016

Study, Year (Reference)	Time Point, *y*	Dose, *mg/d*	Population	OR (95% CI)	Events, *n/N*	
					Aspirin	No Aspirin
PPP, 2001 (23)	3.6	100	Men and women with ≥1 CVD risk factor	0.68 (0.12–3.95)	2/2226	3/2269
HOT, 1998 (24)	3.8	75	Men and women with hypertension	0.93 (0.45–1.93)	14/9399	15/9391
JPAD, 2008 (25)	4.37	81	Men and women with diabetes	0.87 (0.29–2.58)	6/1262	7/1277
PHS, 1989 (26)	5	162.5	Male physicians	1.88 (0.97–3.64)	23/11 037	12/11 034
JPPP, 2014 (31)	5	100	Men and women with ≥1 CVD risk factor	1.84 (1.01–3.35)	28/7220	15/7244
BMD,1988 (27)	6	500	Male physicians	1.08 (0.42–2.81)	13/3429	6/1710
TPT, 1998 (29)	6.8	75	Men at high risk for IHD	3.81 (0.40–36.66)	2.5/1269	0.5/1273
AAA, 2010 (30)	8.2	100	Men and women with ABI ≤0.95	1.25 (0.34–4.62)	5/1675	4/1675
WHS, 2005 (32)	10.1	50	Female health professionals	1.24 (0.83–1.87)	51/19 934	41/19 942
Overall: $I^2 = 0.0\%$; $P = 0.720$				1.33 (1.03–1.71)	144.5/57 451	103.5/55 815



Whitlock et al, Annals of Internal Medicine, 2016

Relative rate ratios for bleeding among subpopulations

Meta-analyses for USPSTF 2016

Baseline Characteristic	Adjusted Incidence Rate Ratio (95% CI)		
	Major GI or Extracranial Bleeding*	Hemorrhagic Stroke†	Hospitalization for Major Bleeding Event‡
Age (per decade)	2.15 (1.93–2.39)	1.59 (1.33–1.90)	1.05 (1.05–1.05)§
Male sex (vs. female sex)	1.99 (1.45–2.73)	1.11 (0.52–2.34)	1.69 (1.61–1.79)
Diabetes (yes vs. no)	1.55 (1.13–2.14)	1.74 (0.95–3.17)	1.36 (1.28–1.44)
Current smoker (yes vs. no)	1.56 (1.25–1.94)	2.18 (1.57–3.02)	
Mean BP (per 20 mm Hg)‖	1.32 (1.09–1.58)	2.18 (1.62–2.87)	
Cholesterol level (per 1 mmol/L)	0.99 (0.90–1.08	0.90 (0.77–1.07)	
BMI (per 5 kg/m^2):	1.24 (1.13–1.35)	0.85 (0.71–1.02)	
Previous GI hospitalization (yes vs. no)	–	–	2.87 (2.46–3.35)
Medication use (yes vs. no)			
NSAID	–	–	1.10 (1.05–1.16)
Aspirin (current vs. never)	–	–	1.61 (1.54–1.69)
Any antihypertensive	–	–	1.14 (1.08–1.19)
Statin	–	–	0.67 (0.62–0.71)
PPI	–	–	0.84 (0.80–0.88)

Whitlock et al, Annals of Internal Medicine, 2016

Summary 2
Harms of aspirin use

- Gastrointestinal bleeding
- Hemorrhagic stroke

Aspirin in CVD secondary prevention

	Number of events (aspirin vs control)		Rate ratio (95% CI) (aspirin vs control)			Yearly absolute difference (% per year)	
	Primary prevention (660 000 person-years)	Secondary prevention (43 000 person-years)	Primary prevention	Secondary prevention	p value for heterogeneity	Primary prevention	Secondary prevention
Major coronary event	934 vs 1115	995 vs 1214	0·82 (0·75–0·90)	0·80 (0·73–0·88)	0·7	−0·06	−1·00*
Non-fatal MI	596 vs 756	357 vs 505	0·77 (0·69–0·86)	0·69 (0·60–0·80)	0·5	−0·05	−0·66
CHD mortality	372 vs 393	614 vs 696	0·95 (0·82–1·10)	0·87 (0·78–0·98)	0·4	−0·01	−0·34
Stroke	655 vs 682	480 vs 580	0·95 (0·85–1·06)	0·81 (0·71–0·92)	0·1	−0·01	−0·46*
Haemorrhagic	116 vs 89	36 vs 19	1·32 (1·00–1·75)	1·67 (0·97–2·90)	0·4	0·01	··†
Ischaemic	317 vs 367	140 vs 176	0·86 (0·74–1·00)	0·78 (0·61–0·99)	0·5	−0·02	··†
Unknown cause	222 vs 226	304 vs 385	0·97 (0·80–1·18)	0·77 (0·66–0·91)	0·1	−0·001	··†
Vascular death	619 vs 637	825 vs 896	0·97 (0·87–1·09)	0·91 (0·82–1·00)	0·4	−0·01	−0·29
Any serious vascular event	1671 vs 1883 (0·51% vs 0·57% per year)	1505 vs 1801 (6·69% vs 8·19% per year)	0·88 (0·82–0·94)	0·81 (0·75–0·87)	0·1	−0·07	−1·49*
Major extracranial bleed	335 vs 219	23 vs 6	1·54 (1·30–1·82)	2·69 (1·25–5·76)	0·2	0·03	··†

Antithrombotic Trialists' (ATT) Collaboration, Lancet 2009

Aspirin in CVD secondary prevention
AHA/ACCF 2011

Class I

1. Aspirin 75–162 mg daily is recommended in all patients with coronary artery disease unless contraindicated.[64,81,82,116] ***(Level of Evidence: A)***
   - Clopidogrel 75 mg daily is recommended as an alternative for patients who are intolerant of or allergic to aspirin.[117] ***(Level of Evidence: B)***
2. A P2Y12 receptor antagonist in combination with aspirin is indicated in patients after ACS or PCI with stent placement.[83–85] ***(Level of Evidence: A)***
   - For patients receiving a bare-metal stent or drug-eluting stent during PCI for ACS, clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice daily should be given for at least 12 months.[84,86,113,114] ***(Level of Evidence: A)***
3. For patients undergoing coronary artery bypass grafting, aspirin should be started within 6 hours after surgery to reduce saphenous vein graft closure. Dosing regimens ranging from 100 to 325 mg daily for 1 year appear to be efficacious.[87–90] ***(Level of Evidence: A)***
4. In patients with extracranial carotid or vertebral atherosclerosis who have had ischemic stroke or TIA, treatment with aspirin alone (75–325 mg daily), clopidogrel alone (75 mg daily), or the combination of aspirin plus extended-release dipyridamole (25 mg and 200 mg twice daily, respectively) should be started and continued.[91,104,116] ***(Level of Evidence: A)***
5. For patients with symptomatic atherosclerotic peripheral artery disease of the lower extremity, antiplatelet therapy with aspirin (75–325 mg daily) or clopidogrel (75 mg daily) should be started and continued.[92,107,116,117] ***(Level of Evidence: A)***

Smith et al, Circulation 2011

Aspirin in CVD secondary prevention AHA/ACCF 2011, cont.

Class IIa

1. If the risk of morbidity from bleeding outweighs the anticipated benefit afforded by thienopyridine therapy after stent implantation, earlier discontinuation (eg, <12 months) is reasonable. ***(Level of Evidence: C)*** (Note: the risk for serious cardiovascular events because of early discontinuation of thienopyridines is greater for patients with drug-eluting stents than those with bare-metal stents.)
2. After PCI, it is reasonable to use 81 mg of aspirin per day in preference to higher maintenance doses.[84,85,118–122] ***(Level of Evidence: B)***
3. For patients undergoing coronary artery bypass grafting, clopidogrel (75 mg daily) is a reasonable alternative in patients who are intolerant of or allergic to aspirin. ***(Level of Evidence: C)***

Class IIb

1. The benefits of aspirin in patients with asymptomatic peripheral artery disease of the lower extremities are not well established.[108,109] ***(Level of Evidence: B)***
2. Combination therapy with both aspirin 75 to 162 mg daily and clopidogrel 75 mg daily may be considered in patients with stable coronary artery disease.[112] ***(Level of Evidence: B)***

Smith et al, Circulation 2011

Recommendations for aspirin in CVD primary prevention
USPSTF 2009, 2016

2009

Men Age 45–79 Years	Women Age 55–79 Years	Men Age <45 Years	Women Age <55 Years	Men and Women Age ≥80 Years
Encourage aspirin use when potential CVD benefit (MIs prevented) outweighs potential harm of GI hemorrhage	Encourage aspirin use when potential CVD benefit (strokes prevented) outweighs potential harm of GI hemorrhage	Do not encourage aspirin use for MI prevention	Do not encourage aspirin use for stroke prevention	No Recommendation
Grade: A		Grade: D		Grade: I (insufficient evidence)

2016, for the primary prevention of CVD and colorectal cancer (CRC)

Adults aged 50 to 59 y with a ≥10% 10-y CVD risk	Adults aged 60 to 69 y with a ≥10% 10-y CVD risk	Adults younger than 50 y	Adults aged 70 y or older
Initiate low-dose aspirin use. Grade: B	The decision to initiate low-dose aspirin use is an individual one. Grade: C	No recommendation. Grade: I (insufficient evidence)	No recommendation. Grade: I (insufficient evidence)

Recommendations for aspirin in CVD primary prevention
AHA/ACC 2002, 2011

2002

- Do not recommend for patients with aspirin intolerance.
- Low-dose aspirin increases risk for gastrointestinal bleeding and hemorrhagic stroke. Do not use in persons at increased risk for these diseases.
- Benefits of cardiovascular risk reduction outweigh these risks in most patients at higher coronary risk. Doses of 75–160 mg/d are as effective as higher doses. Therefore, consider 75–160 mg aspirin per day for persons at higher risk (especially those wit10-y risk of CHD of 10%).

2011, for women (previous versions 2004, 2007)

- Routine use of aspirin in healthy women <65 years of age is not recommended to prevent MI (*Class III, Level of Evidence B*).
- Can be useful in women ≥65 y of age (81 mg daily or 100 mg every other day) if blood pressure is controlled and benefit for ischemic stroke and MI prevention is likely to outweigh risk of gastrointestinal bleeding and hemorrhagic stroke *(Class IIa; Level of Evidence B)*
- May be reasonable for women <65 y of age for ischemic stroke prevention *(Class IIb; Level of Evidence B)*.

Pearson et al, Circulation 2002
Mosca et al, Circulation 2011

Recommendations for aspirin in CVD primary prevention
AHA/ACC 2019

COR	LOE	Recommendations
IIb	A	1. Low-dose aspirin (75-100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk.
III: Harm	B-R	2. Low-dose aspirin (75-100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults >70 years of age.
III: Harm	C-LD	3. Low-dose aspirin (75-100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding.

Arnett et al, Circulation 2019

Recommendations for aspirin in CVD primary prevention
ADA (2016), ACCP (2012), ESC (2016)

American Diabetes Association, 2016

- Use aspirin 75 to 162 mg/d for individuals with diabetes who are not at increased bleeding risk and who have 10-y ASCVD risk>10% (includes most men and women ≥50 y with diabetes and with ≥1 other ASCVD risk factors)
- Individualize for adults with diabetes, <50 y, and multiple ASCVD risk factors (10-y ASCVD risk 5%-10%)
- Not recommended for adults with diabetes who are at low ASCVD risk (10-y risk <5%)

American College of Chest Physicians, 2012

- Suggest aspirin use for adults ≥ 50 y

European Society of Cardiology, 2016

- Not recommended

Diabetes Care, 2016
Vandvik et al, Chest 2016
Piepoli et al, Eur Heart J 2016

Recommendations for aspirin in CVD and CRC primary prevention

USPSTF 2016

Population	Recommendation	Grade (What's This?)
Adults aged 50 to 59 years with a ≥10% 10-year CVD risk	The USPSTF recommends initiating low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer (CRC) in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years.	B
Adults aged 60 to 69 years with a ≥10% 10-year CVD risk	The decision to initiate low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 60 to 69 years who have a 10% or greater 10-year CVD risk should be an individual one. Persons who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years are more likely to benefit. Persons who place a higher value on the potential benefits than the potential harms may choose to initiate low-dose aspirin.	C
Adults younger than 50 years	The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults younger than 50 years.	I
Adults aged 70 years or older	The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults aged 70 years or older.	I

Methods for decision analyses supporting 2016 USPSTF guidelines

Phase 1:

- **Systematic review and meta analyses** on the benefits aspirin in CVD and CRC primary prevention, and risk of serious bleeding

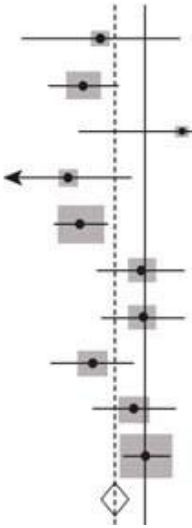
Phase 2:

- **Microsimulation modeling** to assess the net balance of benefits and harms from routine aspirin use across clinically relevant age, sex, and CVD risk groups

Aspirin of any dose: Reduces risk of nonfatal MI

Meta-analyses for USPSTF 2016

Study, Year (Reference)	Aspirin Dose, *mg/d*	Follow-up, *mo*	Population Description	RR (95% CI)	Events, *n/N* IG	Events, *n/N* CG
Nonfatal MI						
PPP, 2001 (38)	100	43.2	Men and women with ≥1 risk factor for CVD	0.69 (0.36–1.33)	15/2226	22/2269
HOT, 1998 (34)	75	45.6	Men and women with hypertension	0.60 (0.45–0.81)	68/9399	113/9391
JPAD, 2008 (35)	100	52.4	Men and women with diabetes	1.35 (0.57–3.19)	12/1262	9/1277
JPPP, 2014 (39)	100	60.2	Men and women with ≥1 risk factor for CVD	0.53 (0.31–0.91)	20/7220	38/7244
PHS I, 1989 (30)	162.5	60.2	Men physicians	0.59 (0.47–0.74)	129/11 037	213/11 034
BMD, 1988 (36)	500	72	Men physicians	0.97 (0.67–1.41)	80/3429	41/1710
POPADAD, 2008 (31)	100	80.4	Men and women with diabetes and ABI ≤0.99	0.98 (0.69–1.40)	55/638	56/638
TPT, 1998 (24)	75	81.6	Men at high risk for ischemic heart disease	0.65 (0.45–0.92)	47/1268	73/1272
AAA, 2010 (33)	100	98.4	Men and women with ABI ≤0.95	0.91 (0.65–1.28)	62/1675	68/1675
WHS, 2005 (37)	50	121.2	Women health professionals	1.01 (0.83–1.24)	184/19 934	181/19 942
Overall: (I^2 = 61.9%; P = 0.005)				0.78 (0.71–0.87)		



1. Collaborative Group of the Primary Prevention Project
2. Principal results of the Hypertension Optimal Treatment
3. Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes
4. Japanese Primary Prevention Project
5. Physicians' Health Study
6. British Male Doctors Trial
7. Prevention of Progression of Arterial Disease and Diabetes
8. Thrombosis Prevention Trial
9. Aspirin for Asymptomatic Atherosclerosis
10. Women's Health Study

Guirguis-Blake et al,
Annals of Internal Medicine 2016

Low-dose aspirin: Similar benefits for nonfatal MI

Meta-analyses for USPSTF 2016

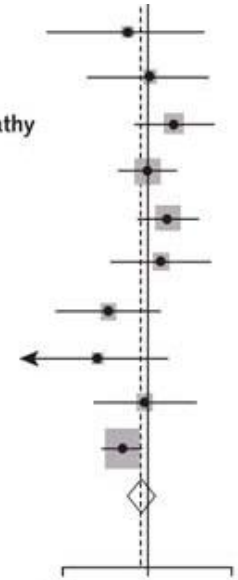
Outcome	Studies, *k*	Participants, *n*	Mantel-Haenszel Fixed-Effects RR (95% CI)	I^2, %
Nonfatal MI	10	114 734	0.78 (0.71–0.87)	61.9
	8	87 524	0.83 (0.74–0.94)	54.5

Guirguis-Blake et al, Annals of Internal Medicine 2016

Aspirin of any dose: No benefits for nonfatal stroke

Meta-analyses for USPSTF 2016

Study, Year (Reference)	Aspirin Dose, *mg/d*	Follow-up, *mo*	Population Description	RR (95% CI)	Events, *n/N* IG	Events, *n/N* CG
PPP, 2001 (38)	100	43.2	Men and women with ≥1 risk factor for CVD	0.84 (0.42–1.07)	15/2220	18/2209
JPAD, 2008 (35)	100	52.4	Men and women with diabetes	1.01 (0.60–1.72)	27/1262	27/1277
ETDRS, 1992 (32)	650	60	Men and women with diabetes and diabetic retinopathy	1.26 (0.89–1.80)	67/1856	53/1855
JPPP, 2014 (39)	100	60.2	Men and women with ≥1 risk factor for CVD	1.00 (0.77–1.31)	109/7220	109/7244
PHS I, 1989 (30)	162.5	60.2	Men physicians	1.20 (0.91–1.59)	110/11 037	92/11 034
BMD, 1988 (36)	500	72	Men physicians	1.13 (0.72–1.77)	61/3429	27/1710
POPADAD, 2008 (31)	100	80.4	Men and women with diabetes and ABI ≤0.99	0.71 (0.45–1.12)	29/638	41/638
TPT, 1998 (24)	75	81.6	Men at high risk for ischemic heart disease	0.64 (0.34–1.20)	18/1280	25/1272
AAA, 2010 (33)	100	98.4	Men and women with ABI ≤0.95	0.97 (0.62–1.52)	37/1675	38/1675
WHS, 2005 (37)	50	121.2	Women health professionals	0.81 (0.67–0.97)	198/19 934	244/19 942
Overall: (I^2 = 25.1%; P = 0.212)				0.95 (0.85–1.06)		



Guirguis-Blake et al, Annals of Internal Medicine 2016

Low-dose aspirin: Some benefits for nonfatal stroke

Meta-analyses for USPSTF 2016

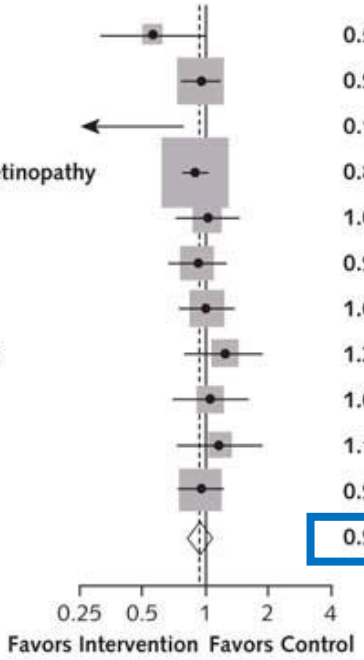
Outcome	Studies, *k*	Participants, *n*	Mantel-Haenszel Fixed-Effects RR (95% CI)	I^2, %
Nonfatal MI	10	114 734	0.78 (0.71-0.87)	61.9
	8	87 524	0.83 (0.74-0.94)	54.5
Nonfatal stroke	10	99 655	0.95 (0.85-1.06)	25.1
	7	68 734	0.86 (0.76-0.98)	0

Guirguis-Blake et al, Annals of Internal Medicine 2016

Aspirin of any dose: No benefits for CVD mortality

Meta-analyses for USPSTF 2016

Study, Year (Reference)	Aspirin Dose, *mg/d*	Follow-up, *mo*	Population Description	RR (95% CI)	Events, *n/N* IG	Events, *n/N* CG
CVD mortality						
PPP, 2001 (38)	100	43.2	Men and women with ≥1 risk factor for CVD	0.56 (0.31–1.01)	17/2226	31/2269
HOT, 1998 (34)	75	45.6	Men and women with hypertension	0.95 (0.75–1.20)	133/9399	140/9391
JPAD, 2008 (35)	100	52.4	Men and women with diabetes	0.10 (0.01–0.79)	1/1262	10/1277
ETDRS, 1992 (32)	650	60	Men and women with diabetes and diabetic retinopathy	0.89 (0.76–1.04)	244/1856	275/1855
JPPP, 2014 (39)	100	60.2	Men and women with ≥1 risk factor for CVD	1.02 (0.71–1.47)	58/7220	57/7244
PHS I, 1989 (30)	162.5	60.2	Men physicians	0.92 (0.66–1.28)	66/11 037	72/11 034
BMD, 1988 (36)	500	72	Men physicians	1.01 (0.74–1.37)	119/3429	59/1710
POPADAD, 2008 (31)	100	80.4	Men and women with diabetes and ABI ≤0.99	1.23 (0.80–1.89)	43/638	35/638
TPT, 1998 (24)	75	81.6	Men at high risk for ischemic heart disease	1.05 (0.69–1.61)	42/1268	40/1272
AAA, 2010 (33)	100	98.4	Men and women with ABI ≤0.95	1.17 (0.72–1.89)	35/1675	30/1675
WHS, 2005 (37)	50	121.2	Women health professionals	0.95 (0.74–1.22)	120/19 934	126/19 942
Overall: (I^2 = 8.8%; P = 0.360)				0.94 (0.86–1.03)		



Guirguis-Blake et al, Annals of Internal Medicine 2016

Low-dose aspirin: No benefits for CVD mortality

Meta-analyses for USPSTF 2016

Outcome	Studies, *k*	Participants, *n*	Mantel-Haenszel Fixed-Effects RR (95% CI)	I^2, %
Nonfatal MI	10	114 734	0.78 (0.71-0.87)	61.9
	8	87 524	0.83 (0.74-0.94)	54.5
Nonfatal stroke	10	99 655	0.95 (0.85-1.06)	25.1
	7	68 734	0.86 (0.76-0.98)	0
CVD mortality	11	118 445	0.94 (0.86-1.03)	8.8
	8	87 524	0.97 (0.85-1.10)	30.0

Guirguis-Blake et al, Annals of Internal Medicine 2016

Duration and formulation

Meta-analyses for USPSTF 2016

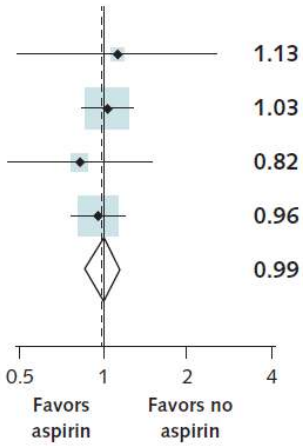
- **Duration:** Overall, available data (9 RCTs) suggest that any CVD benefit from aspirin begins within the first 1 to 5 years.
  - no clear upper time limit to benefit because of inconsistent results and relatively short trial durations.
- **Formulation:** No conclusions can be made about treatment formulation, which reflects the heterogeneity of trial design and sparse reporting of tablet formation in some trials.

Aspirin reduces risk of CRC after 10 y

Meta-analyses for USPSTF 2016

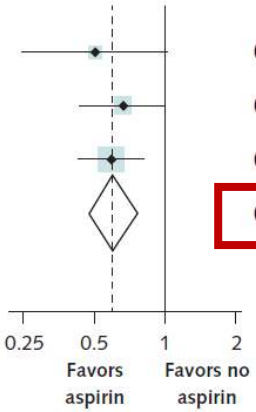
0-12 y

Study, Year (Reference)	Mean or Median Treatment Duration, *y*	Dose, *mg/d*	Population	RR (95% CI)	Events, *n/N* Aspirin	Events, *n/N* No Aspirin
Farrell et al, 1991 (UK-TIA) (64)	4.4	300 or 1200	Recent TIA or stroke	1.13 (0.49–2.58)	18/1632	8/817
Stürmer et al, 1998 (PHS) (70)	5.0	162.5	Male physicians	1.03 (0.83–1.27)	173/11 037	168/11 034
Peto et al, 1988 (BMD) (54)	6.0	500	Male physicians	0.82 (0.45–1.50)	28/3429	17/1710
Cook et al, 2013 (WHS) (69)	10.1	50	Female health professionals	0.96 (0.76–1.21)	144/19 934	150/19 942
Overall ($I^2 = 0.0\%$, $P = 0.88$)				0.99 (0.85–1.15)	363/36 032	343/33 503



10-19 y

Farrell et al, 1991 (UK-TIA) (64)	4.4	300 or 1200	Recent TIA or stroke	0.50 (0.25–1.02)	15/1632	15/817
Peto et al, 1988 (BMD) (54)	6.0	500	Male physicians	0.66 (0.43–1.00)	50/3429	38/1710
Cook et al, 2013 (WHS) (69)	10.1	50	Female health professionals	0.59 (0.42–0.81)	58/19 934	99/19 942
Overall ($I^2 = 0.0\%$, $P = 0.80$)				0.60 (0.47–0.76)	123/24 995	152/22 469



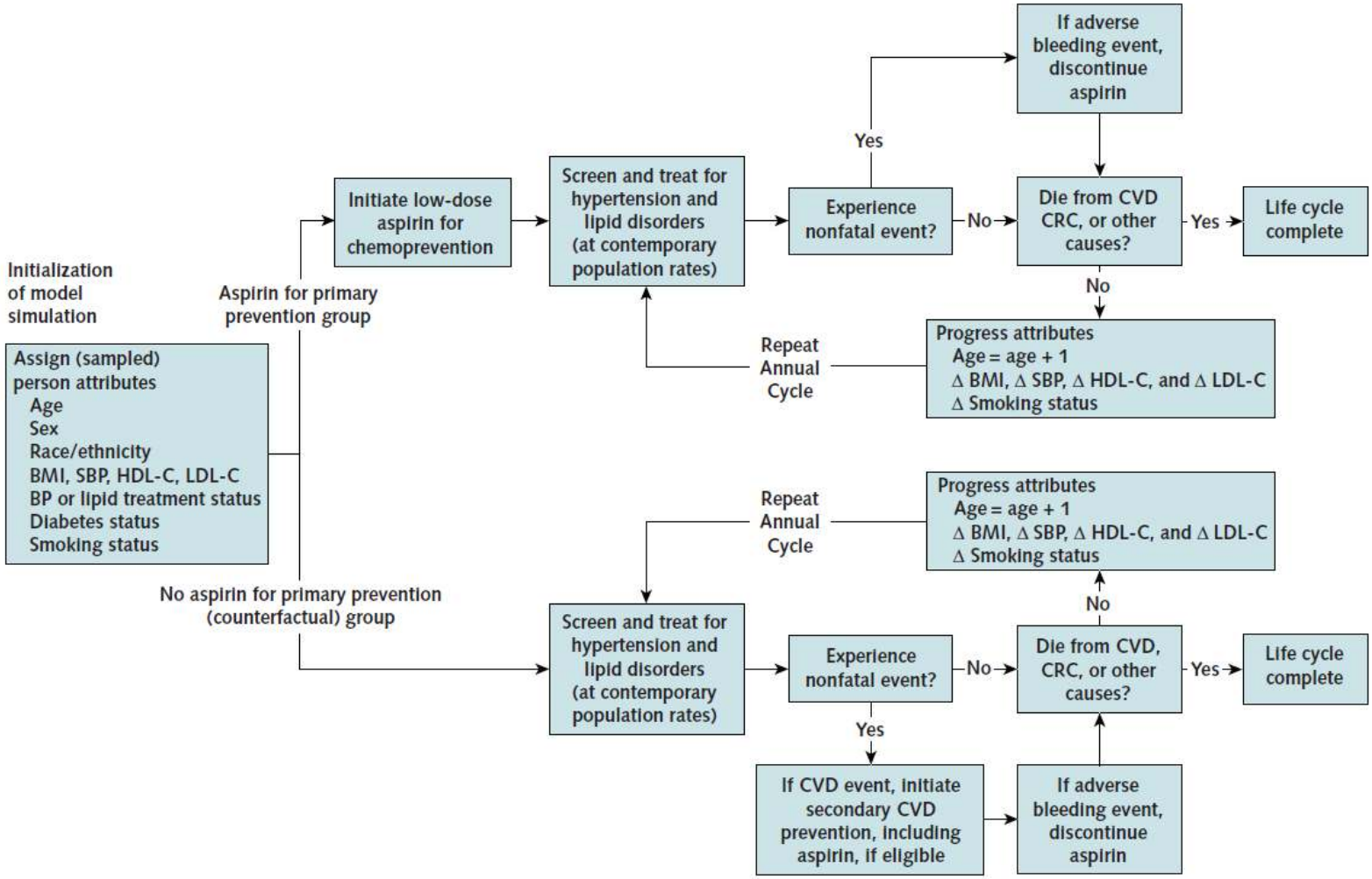
Chubak et al, Annals of Internal Medicine 2016

Phase 1: Parameters associated with benefit and harm of aspirin use

Meta-analyses for USPSTF 2016

Parameter	RR				Reference
	Base Case	Worst Case	Best Case	Other Values	
Benefits					
CRC incidence (>10 y)	0.60	0.76	0.47	1.00	13, 35, 36
CVD death	1.00	1.00	0.85	0.97	12, 27–34
Nonfatal ischemic stroke	0.86	0.98	0.76		12, 27, 29–34
Nonfatal MI	0.83	0.94	0.74		12, 27–34
Harms					
Major GI bleeding	1.58	1.95	1.29		14, 27–29, 32, 33
Hemorrhagic stroke	1.27	1.68	1.00		14, 27–29, 31–34

Phase 2: Decision analyses to assess the net balance of benefits and harms from routine aspirin use across clinically relevant age, sex, and CVD risk groups



Dehmer et al, Annals of Internal Medicine 2016

Net life-years and QALYs of lifetime, 20-y, and 10-y aspirin use, USPSTF 2016

10-y CVD Risk, %	Initiation Age 40-49 y			Initiation Age 50-59 y			Initiation Age 60-69 y			Initiation Age 70-79 y		
	Lifetime	20 y	10 y	Lifetime	20 y	10 y	Lifetime	20 y	10 y	Lifetime	20 y	10 y
Men												
Net life-years per 1000 persons												
1	**28.0**	**−1.8**	**−0.5**	**13.2**	**−5.5**	**−1.0**	NA	NA	NA	NA	NA	NA
5	**48.9**	**−2.7**	**−0.7**	**15.3**	**−6.2**	**−1.8**	−5.7	**−11.0**	**−3.2**	NA	NA	NA
10	**71.0**	−1.9	**−1.1**	**33.3**	−2.8	**−2.1**	−2.0	**−10.0**	**−4.2**	**−15.0**	**−16.2**	**−6.5**
15	**82.8**	0.7	**−1.3**	**39.5**	−2.2	**−2.6**	**9.6**	**−5.3**	**−3.9**	**−18.0**	**−18.1**	**−6.1**
20	**80.1**	1.4	**−0.8**	**60.5**	**7.4**	**−1.1**	**11.6**	**−7.5**	**−5.1**	**−22.5**	**−22.3**	**−9.8**
Net QALYs per 1000 persons												
1	**51.7**	0.1	**−0.8**	**36.8**	0.1	**−1.1**	NA	NA	NA	NA	NA	NA
5	**74.1**	**4.2**	−0.1	**40.0**	**2.6**	**−1.4**	**16.1**	0.1	**−2.8**	NA	NA	NA
10	**97.2**	**8.7**	0.5	**58.8**	**10.1**	−0.4	**18.0**	1.9	**−2.9**	−1.0	**−4.7**	**−4.9**
15	**107.9**	**11.6**	0.7	**64.4**	**12.8**	0.0	**30.9**	**10.1**	**−1.3**	−3.1	**−5.7**	**−4.5**
20	**105.7**	**14.2**	**2.0**	**83.4**	**23.6**	**3.0**	**31.8**	**8.8**	**−1.7**	**−6.2**	**−8.4**	**−6.8**
Women												
Net life-years per 1000 persons												
1	3.2	**−1.7**	−0.3	**−9.6**	**−5.3**	**−0.9**	**−18.0**	**−7.9**	**−2.4**	NA	NA	NA
5	**41.7**	**−2.1**	**−0.7**	**10.0**	**−7.8**	**−2.2**	**−12.0**	**−10.0**	**−2.7**	**−23.4**	**−17.1**	**−3.4**
10	**59.0**	−1.2	**−0.6**	**21.9**	**−6.4**	**−2.5**	−1.2	**−10.0**	**−3.2**	**−25.1**	**−20.5**	**−5.0**
15	**57.3**	0.4	−0.3	**33.4**	**−3.6**	**−2.0**	1.7	**−11.0**	**−4.4**	**−22.0**	**−22.2**	**−6.6**
20	**67.7**	−0.6	**−0.7**	**46.3**	−2.6	**−2.3**	4.8	**−7.9**	**−4.9**	**−26.1**	**−24.3**	**−7.8**
Net QALYs per 1000 persons												
1	**36.6**	**1.4**	−0.3	**21.8**	−0.2	**−1.0**	**7.4**	−0.7	**−2.6**	NA	NA	NA
5	**78.4**	**5.2**	0.1	**45.0**	**4.2**	**−0.8**	**16.4**	2.2	**−1.5**	−4.4	**−6.1**	**−2.9**
10	**96.9**	**8.7**	**0.9**	**62.1**	**10.2**	0.1	**28.4**	**6.6**	−0.4	−4.4	**−6.1**	**−3.1**
15	**98.4**	**11.3**	**1.7**	**71.6**	**15.0**	**1.6**	**32.4**	**9.3**	0.1	−1.5	**−6.4**	**−4.0**
20	**106.5**	**10.3**	**1.2**	**83.3**	**16.8**	**1.5**	**36.0**	**13.0**	0.3	−2.7	**−5.5**	**−3.6**

Dehmer et al, Annals of Internal Medicine 2016

Lifetime events in 10,000 adults, USPSTF 2016

Table 1. Lifetime Events in 10,000 Men Taking Aspirin*

CVD Risk	Nonfatal MIs Prevented	Nonfatal Ischemic Strokes Prevented	CRC Cases Prevented	Serious GI Bleeding Caused	Hemorrhagic Strokes Caused	Net Life-Years Gained	QALYs Gained
Aged 50 to 59 years							
10%	225	84	139	284	23	333	588
15%	267	86	121	260	28	395	644
20%	286	92	122	248	21	605	834
Aged 60 to 69 years							
10%	159	66	112	314	31	-20	180
15%	186	80	104	298	24	96	309
20%	201	84	91	267	27	116	318

Table 2. Lifetime Events in 10,000 Women Taking Aspirin*

CVD Risk	Nonfatal MIs Prevented	Nonfatal Ischemic Strokes Prevented	CRC Cases Prevented	Serious GI Bleeding Caused	Hemorrhagic Strokes Caused	Net Life-Years Gained	QALYs Gained
Aged 50 to 59 years							
10%	148	137	139	209	35	219	621
15%	150	143	135	200	34	334	716
20%	152	144	132	184	29	463	833
Aged 60 to 69 years							
10%	101	116	105	230	32	-12	284
15%	110	129	93	216	34	17	324
20%	111	130	97	217	33	48	360

2016 USPSTF guideline on aspirin use for primary prevention of CVD and CRC

Population	Recommendation	Grade (What's This?)
Adults aged 50 to 59 years with a ≥10% 10-year CVD risk	The USPSTF recommends initiating low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer (CRC) in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years.	B
Adults aged 60 to 69 years with a ≥10% 10-year CVD risk	The decision to initiate low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 60 to 69 years who have a 10% or greater 10-year CVD risk should be an individual one. Persons who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years are more likely to benefit. Persons who place a higher value on the potential benefits than the potential harms may choose to initiate low-dose aspirin.	C
Adults younger than 50 years	The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults younger than 50 years.	I
Adults aged 70 years or older	The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults aged 70 years or older.	I

Aspirin in CVD primary prevention ACC/AHA 2019

COR	LOE	Recommendations
IIb	A	1. Low-dose aspirin (75-100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk.

CLASS IIa (MODERATE) **Benefit >> Risk**

Suggested phrases for writing recommendations:

- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

LEVEL (QUALITY) OF EVIDENCE‡

Level A

- High-quality evidence‡ from more than 1 RCTs
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

Aspirin in CVD primary prevention ACC/AHA 2019

COR	LOE	Recommendations
IIb	A	1. Low-dose aspirin (75-100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk.
III: Harm	B-R	2. Low-dose aspirin (75-100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults >70 years of age.

CLASS III: Harm (STRONG) **Risk > Benefit**

Suggested phrases for writing recommendations:

- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

Level B-R **(Randomized)**

- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

Aspirin in CVD primary prevention ACC/AHA 2019

COR	LOE	Recommendations
IIb	A	1. Low-dose aspirin (75-100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk.
III: Harm	B-R	2. Low-dose aspirin (75-100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults >70 years of age.
III: Harm	C-LD	3. Low-dose aspirin (75-100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding.

CLASS III: Harm (STRONG) **Risk > Benefit**

Suggested phrases for writing recommendations:

- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

Level C-LD **(Limited Data)**

- Randomized or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies
- Physiological or mechanistic studies in human subjects

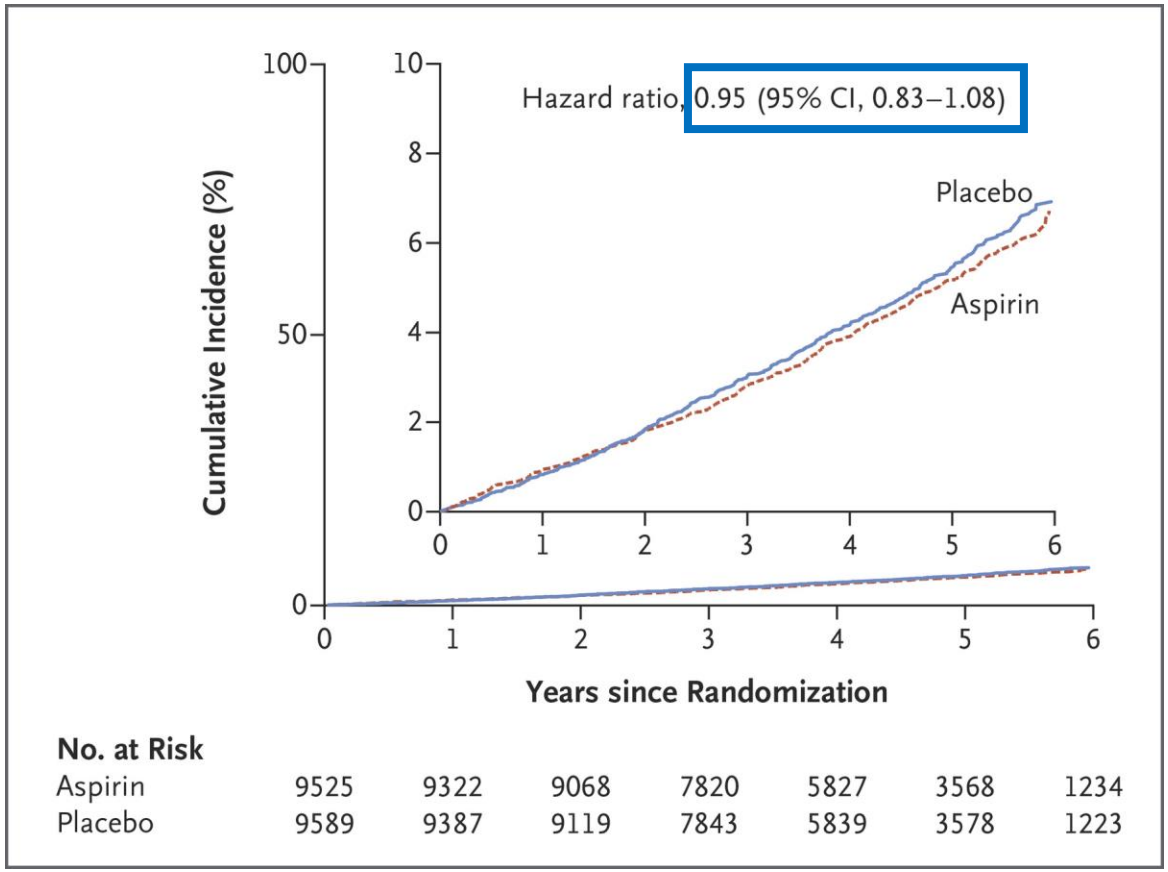
Rationale for lower COR (Class IIb) and removal of specific PCE threshold for aged 40-70, ACC/AHA 2019

- The relative benefits of aspirin, specifically in preventing nonfatal MI and perhaps stroke (with a trend to lower mortality) have been less evident in more recent trials (S4.6-9, S4.6-16, S4.6-17, S4.6-20).

ASPREE, no difference in CVD incidence among aged 65+

(AUS/US, 2010-, aged 70+, N=19,114, 4.7 years, daily 100mg)

Prespecified secondary end point of cardiovascular disease: a composite of fatal coronary heart disease, nonfatal MI, fatal or nonfatal stroke, or hospitalization for heart failure.



McNeil JJ et al, N Engl J Med. 2018

ASPREE, no difference in major adverse cardiovascular events among aged 65+

(AUS/US, 2010-, aged 70+, N=19,114, 4.7 years, daily 100mg)

Table 2. Cardiovascular Events.*

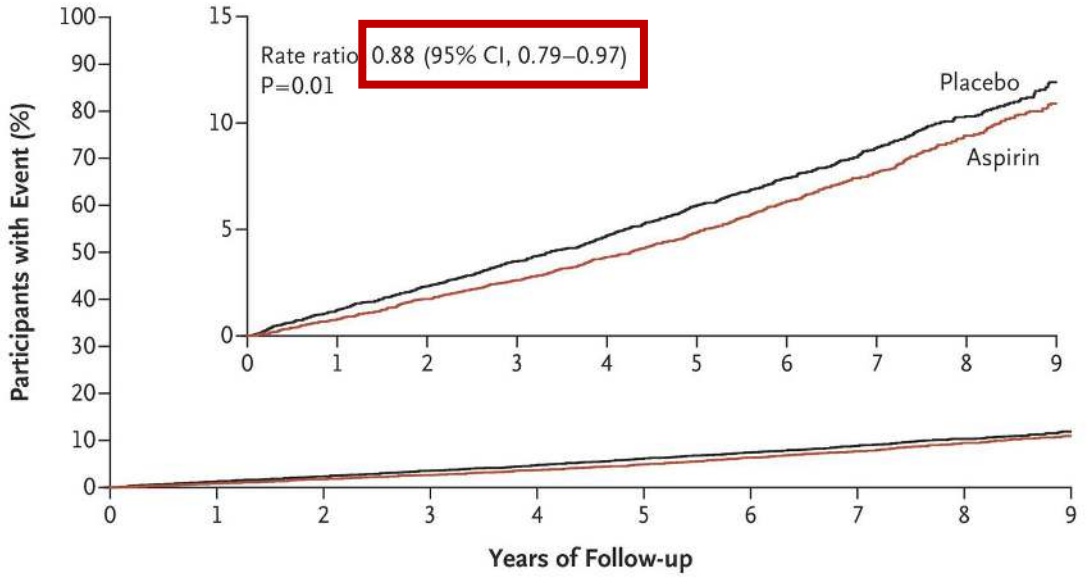
End Point	Overall (N=19,114)	Aspirin (N=9525)		Placebo (N=9589)		Hazard Ratio (95% CI)
	no. of participants with event	*no. of participants with event*	*rate per 1000 person-yr*	*no. of participants with event*	*rate per 1000 person-yr*	
Cardiovascular disease†	922	448	10.7	474	11.3	0.95 (0.83–1.08)
Major adverse cardiovascular event‡	701	329	7.8	372	8.8	0.89 (0.77–1.03)
Fatal cardiovascular disease§	159	78	1.8	81	1.9	0.97 (0.71–1.33)
Hospitalization for heart failure	171	88	2.1	83	1.9	1.07 (0.79–1.44)
Fatal or nonfatal myocardial infarction	355	171	4.0	184	4.3	0.93 (0.76–1.15)
Fatal or nonfatal ischemic stroke¶	315	148	3.5	167	3.9	0.89 (0.71–1.11)

Nonprespecified end point of major adverse cardiovascular events: a composite of fatal coronary heart disease, nonfatal MI, or fatal or nonfatal ischemic stroke.

McNeil JJ et al, N Engl J Med. 2018

ASCEND, lower incidence of first serious vascular events among diabetes

(UK, 2010-, aged 40+, N=15,480, 7.4 years, daily 100mg)



No. at Risk										
Placebo	7740	7618	7486	7342	7188	7001	5771	3890	2200	1430
Aspirin	7740	7655	7536	7404	7252	7096	5825	3966	2222	1428
Cumulative benefit per 1000 participants in aspirin group		4±2	6±2	9±3	10±3	13±4	11±4	12±5	9±6	10±7

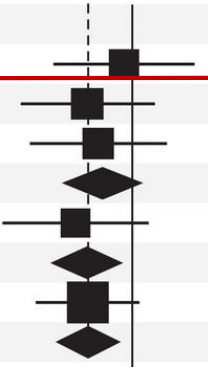
First serious vascular event:
nonfatal MI, nonfatal stroke (excluding confirmed intracranial hemorrhage)
or transient ischemic attack, or death from any vascular cause (excluding confirmed intracranial hemorrhage)

Bowman L et al, N Engl J Med. 2018

ASCEND, no difference on nonfatal MI among diabetes

(UK, 2010-, aged 40+, N=15,480, 7.4 years, daily 100mg)

Type of Event	Aspirin (N=7740)	Placebo (N=7740)	Rate Ratio (95% CI)	P Value
	no. of participants with event (%)			
Vascular Outcomes				
Nonfatal myocardial infarction	191 (2.5)	195 (2.5)	0.98 (0.80–1.19)	
Nonfatal presumed ischemic stroke	202 (2.6)	229 (3.0)	0.88 (0.73–1.06)	
Vascular death excluding intracranial hemorrhage	197 (2.5)	217 (2.8)	0.91 (0.75–1.10)	
Any serious vascular event excluding TIA	**542 (7.0)**	**587 (7.6)**	**0.92 (0.82–1.03)**	
TIA	168 (2.2)	197 (2.5)	0.85 (0.69–1.04)	
Any serious vascular event including TIA	**658 (8.5)**	**743 (9.6)**	**0.88 (0.79–0.97)**	**0.01**
Any arterial revascularization	340 (4.4)	384 (5.0)	0.88 (0.76–1.02)	
Any serious vascular event or revascularization	**833 (10.8)**	**936 (12.1)**	**0.88 (0.80–0.97)**	



Bowman L et al, N Engl J Med. 2018

ARRIVE, aspirin among individuals with moderate predicted risk of CVD

(7 countries, 2007-, aged 55+[M]/60+ [F], N=12,546, 5 years, daily 100mg)

	Aspirin (n=6270)	Placebo (n=6276)
Mean age, years	63·9 (7·1)	63·9 (7·1)
Sex		
Female	1851 (29·5%)	1857 (29·6%)
Male	4419 (70·5%)	4419 (70·4%)
Race		
White	6133 (97·8%)	6146 (97·9%)
Other	137 (2·2%)	130 (2·1%)
Current cigarette smoker*	1808 (28·8%)	1786 (28·5%)
Median weight, kg	82·0 (35–163)	82·0 (43–177)
Mean body-mass index	28·3 (4·3)	28·5 (4·3)
High total cholesterol†	3647 (58·2%)	3657 (58·3%)
High LDL‡	2775 (44·3%)	2869 (45·7%)
Low HDL§	857 (13·7%)	875 (13·9%)
High systolic blood pressure¶	3916 (62·5%)	3950 (62·9%)
Median systolic blood pressure	145·0 (80–199)	145·0 (95–215)
Taking anti-hypertensive medications	4038 (64·4%)	4097 (65·3%)
Mean estimate ACC/AHA 10-year ASCVD risk score at baseline	17·3% (9·8)	17·4% (9·7)

Gaziano JM et al, Lancet. 2018

ARRIVE, no CVD benefits among individuals with "moderate" predicted risk of CVD (10-year actual risk <10%)

(7 countries, 2007-, aged 55+[M]/60+ [F], N=12,546, 5 years, daily 100mg)

	Number of events in the intention-to-treat population			Number of events in the per-protocol population		
	Aspirin (n=6270)	Placebo (n=6276)	Hazard ratio (95% CI); p value	Aspirin (n=3790)	Placebo (n=3912)	Hazard ratio (95% CI); p value
Myocardial infarction, stroke, cardiovascular death, unstable angina, or transient ischaemic attack	269 (4·29%)	281 (4·48%)	0·96 (0·81–1·13); p=0·6038	129 (3·40%)	164 (4·19%)	0·81 (0·64–1·02); p=0·0756
Myocardial infarction, stroke, or cardiovascular death	208 (3·32%)	218 (3·47%)	0·95 (0·79–1·15); p=0·6190	103 (2·72%)	135 (3·45%)	0·79 (0·61–1·02); p=0·0661
Myocardial infarction*	95 (1·52%)	112 (1·78%)	0·85 (0·64–1·11); p=0·2325	37 (0·98%)	72 (1·84%)	0·53 (0·36–0·79); p=0·0014
Non-fatal myocardial infarction	88 (1·40%)	98 (1·56%)	0·90 (0·67–1·20); p=0·4562	32 (0·84%)	60 (1·53%)	0·55 (0·36–0·84); p=0·0056
Stroke*	75 (1·20%)	67 (1·07%)	1·12 (0·80–1·55); p=0·5072	40 (1·06%)	37 (0·95%)	1·12 (0·71–1·75); p=0·6291
Cardiovascular death	38 (0·61%)	39 (0·62%)	0·97 (0·62–1·52); p=0·9010	26 (0·69%)	26 (0·66%)	1·03 (0·60–1·77); p=0·9161
Unstable angina	20 (0·32%)	20 (0·32%)	1·00 (0·54–1·86); p=0·9979	8 (0·21%)	11 (0·28%)	0·75 (0·30–1·87); p=0·5380
Transient ischaemic attack	42 (0·67%)	45 (0·72%)	0·93 (0·61–1·42); p=0·7455	19 (0·50%)	19 (0·49%)	1·03 (0·55–1·95); p=0·9181
Any death	160 (2·55%)	161 (2·57%)	0·99 (0·80–1·24); p=0·9459	108 (2·85%)	101 (2·58%)	1·10 (0·84–1·45); p=0·4796

Gaziano JM et al, Lancet. 2018

Rationale for lower COR (Class IIb) and removal of specific PCE threshold for aged 40-70, ACC/AHA 2019

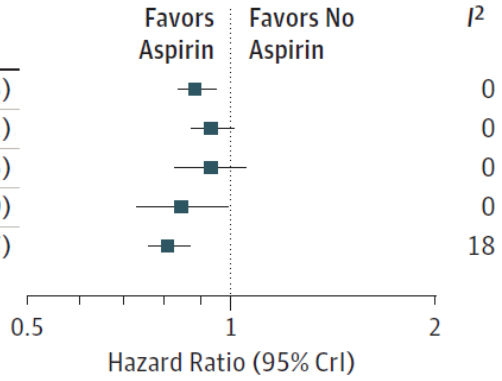
- The relative benefits of aspirin, specifically in preventing nonfatal MI and perhaps stroke (with a trend to lower mortality) have been less evident in more recent trials.
- The need to consider the totality of available evidence for ASCVD
  - Strong family history of premature MI
  - Inability to achieve lipid or BP or glucose targets
  - Significant elevation in coronary artery calcium score
- Tailored decisions based upon patient and clinical preferences

Summary 3
Recent guidelines on aspirin in primary prevention of CVD (and CRC)

- **USPSTF 2016**
  - Age 50-69 with >10% 10-y CVD risk based on PCE
  - Based on net benefits estimated through systematic review & meta-analyses, and decision modeling
  - The first time that primary prevention for CRC was endorsed
  - Stratified by age, sex, 10-y CVD risk
  - Estimates for older ages were unreliable and based largely on a trial of alternate-day rather than daily aspirin
  - Not stratified by baseline CRC risk
- **AHA/ACC 2019**
  - Age 40-70 with higher risk of ASCVD
  - Removed PCE risk threshold
  - Qualitative evaluation that incorporated recent findings from 3 RCTs (ASPREE, ASCEND, ARRIVE) including 1 RCT among the elderly

The most recent meta-analyses published in JAMA

Cardiovascular Outcomes	No. of Studies	Aspirin		No Aspirin		Absolute Risk Reduction, % (95% CI)	HR (95% CrI)
		No. of Events	No. of Participants	No. of Events	No. of Participants		
Composite CV outcome	11	2911	79717	3072	78147	0.38 (0.20 to 0.55)	0.89 (0.84-0.95)
All-cause mortality	13	3622	81623	3588	80057	0.13 (-0.07 to 0.32)	0.94 (0.88-1.01)
CV mortality	13	995	81623	997	80057	0.07 (-0.04 to 0.17)	0.94 (0.83-1.05)
Myocardial infarction	13	1469	81623	1599	80057	0.28 (0.05 to 0.47)	0.85 (0.73-0.99)
Ischemic stroke	10	831	65316	942	63752	0.16 (0.06 to 0.30)	0.81 (0.76-0.87)

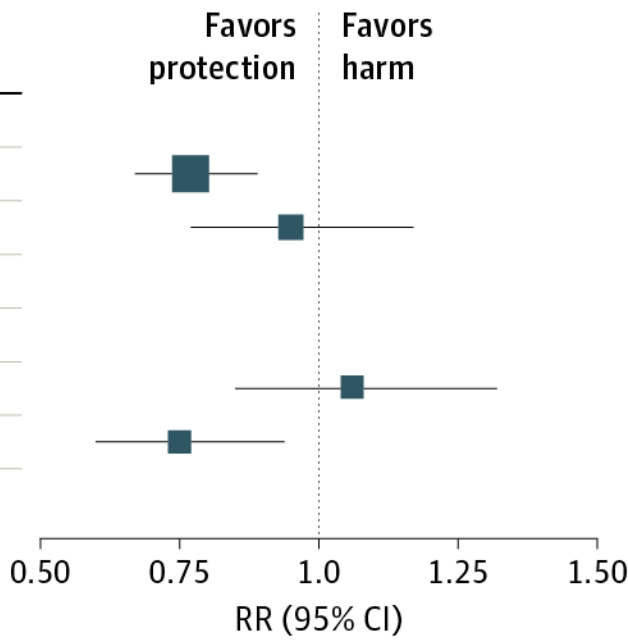


Zheng et al, JAMA 2019

Future directions

- Precision prevention
  - Sex

Subgroup	Events (%/y) Allocated Aspirin	Allocated Control	RR (95% CI)
Major coronary events			
Men	635 (0.57%/y)	801 (0.72%/y)	0.77 (0.67-0.89)
Women	299 (0.14%/y)	314 (0.14%/y)	0.95 (0.77-1.17)
P for interaction = .03			
Ischemic stroke			
Men	312 (0.28%/y)	292 (0.26%/y)	1.06 (0.85-1.32)
Women	227 (0.10%/y)	301 (0.14%/y)	0.75 (0.60-0.94)
P for interaction = .005			



Mora S et al, JAMA Internal Medicine 2016

Future directions

- Precision prevention
  - Sex
  - Risk assessment
    - Improved ASCVD risk assessment

ASCVD risk calculators

Risk Assessment Tool	Variables Included	Outcomes Predicted	Derivation Sample	Features	Comments About Implementation
Pooled cohort equations http://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/ (42) https://professional.heart.org/professional/GuidelinesStatements/PreventionGuidelines/UCM_457698_ASCVD-Risk-Calculator.jsp (43)	• Age • Sex • Race • Total cholesterol • HDL-C • SBP • Antihypertensive therapy • History of diabetes mellitus • Current smoking	Hard ASCVD (CHD death, nonfatal MI, fatal or nonfatal stroke)	5 community-based cohorts of white and black participants	Sex- and race-specific equations for 4 groups: white men, white women, black men, black women	• Available in apps/online and in some electronic health record platforms • Uncertain utility in other racial/ethnic groups • Data available for reclassification by CAC score
Framingham General CVD Risk Profile https://reference.medscape.com/calculator/framingham-cardiovascular-disease-risk (44)	• Age • Sex • Total cholesterol • HDL-C • SBP • Antihypertensive therapy • History of diabetes mellitus • Current smoking	Total CVD (CHD death, MI, coronary insufficiency, angina, ischemic stroke, hemorrhagic stroke, transient ischemic attack, intermittent claudication, and heart failure)	Single community-based cohort of 2 generations	Sex-specific equations for whites	• Available online • Uncertain utility in other racial/ethnic groups • Uncertain calibration to hard ASCVD endpoint • Uncertain reclassification by CAC score
Reynolds Risk Score http://www.reynoldsriskscore.org/ (45, 46)	• Age • Sex • Total cholesterol • HDL-C • SBP • Current smoking • hsCRP level • Parental history of MI before age 60 y	Expanded ASCVD (CHD death, nonfatal MI, fatal or nonfatal stroke, coronary revascularization)	Largely white health professionals enrolled in clinical trials	Sex-specific equations	• Available online • Uncertain utility in other racial/ethnic groups • Uncertain calibration to hard ASCVD endpoint • Uncertain reclassification by CAC score

Lloyd-Jones et al, JACC, 2018

Future directions

- Precision prevention
  - Sex
  - Risk assessment
    - Improved ASCVD risk assessment
    - Baseline CRC risk assessment

NCI CRC risk assessment tool for men aged ≥50

Variable	Proximal		Distal		Rectal*	
	OR	95% CI	OR	95% CI	OR	95% CI
Sigmoidoscopy and/or colonoscopy and polyp history						
Sigmoidoscopy and/or colonoscopy in last 10 years, and no history of polyps	1.00		1.00		1.00	
No sigmoidoscopy and/or colonoscopy in last 10 years	1.42	1.09 to 1.88	2.83	2.10 to 3.81	3.86	2.71 to 5.48
Sigmoidoscopy and/or colonoscopy in last 10 years and history of polyps	1.77	1.17 to 2.66	1.34	0.82 to 2.21	1.92	1.07 to 3.45
Sigmoidoscopy and/or colonoscopy and polyps unknown	1.58	1.02 to 2.41	2.61	1.72 to 3.97	0.51	0.14 to 1.81
No. of relatives with CRC						
0	1.00		1.00		1.00	
1	1.81	1.35 to 2.42	1.68	1.24 to 2.27	1.49	0.91 to 2.46
≥ 2	3.28	1.84 to 5.84	2.81	1.53 to 5.16		
Current leisure-time activity, h/wk						
0					1.00	
> 0 and ≤ 2					0.83	0.72 to 0.95
> 2 and ≤ 4					0.69	0.52 to 0.90
> 4					0.57	0.38 to 0.85
Aspirin/NSAID use						
Nonuser	1.00		1.00		1.00	
Regular user	0.65	0.51 to 0.82	0.71	0.57 to 0.90	0.66	0.46 to 0.95
Smoking, cigarettes/d						
Never smoker	1.00					
> 0 and < 11	1.30	1.05 to 1.61				
≥ 11 and ≤ 20	1.70	1.11 to 2.60				
> 20	2.22	1.17 to 4.20				
Years of smoking						
0	1.00					
> 0 and < 15	0.60	0.34 to 1.06				
≥ 15 and < 35	0.88	0.50 to 1.55				
≥ 35	0.67	0.38 to 1.21				
Vegetable intake, servings/d						
< 5	1.00					
≥ 5	0.58	0.41 to 0.80				
Body mass index, kg/m^2						
≤ 24.9	1.00		1.00			
25.0 to ≤ 30	1.26	1.07 to 1.49	1.38	1.17 to 1.62		
> 30	1.59	1.14 to 2.21	1.90	1.38 to 2.61		

Freedman *et al*, JCO 2009

NCI CRC risk assessment tool for women aged ≥50

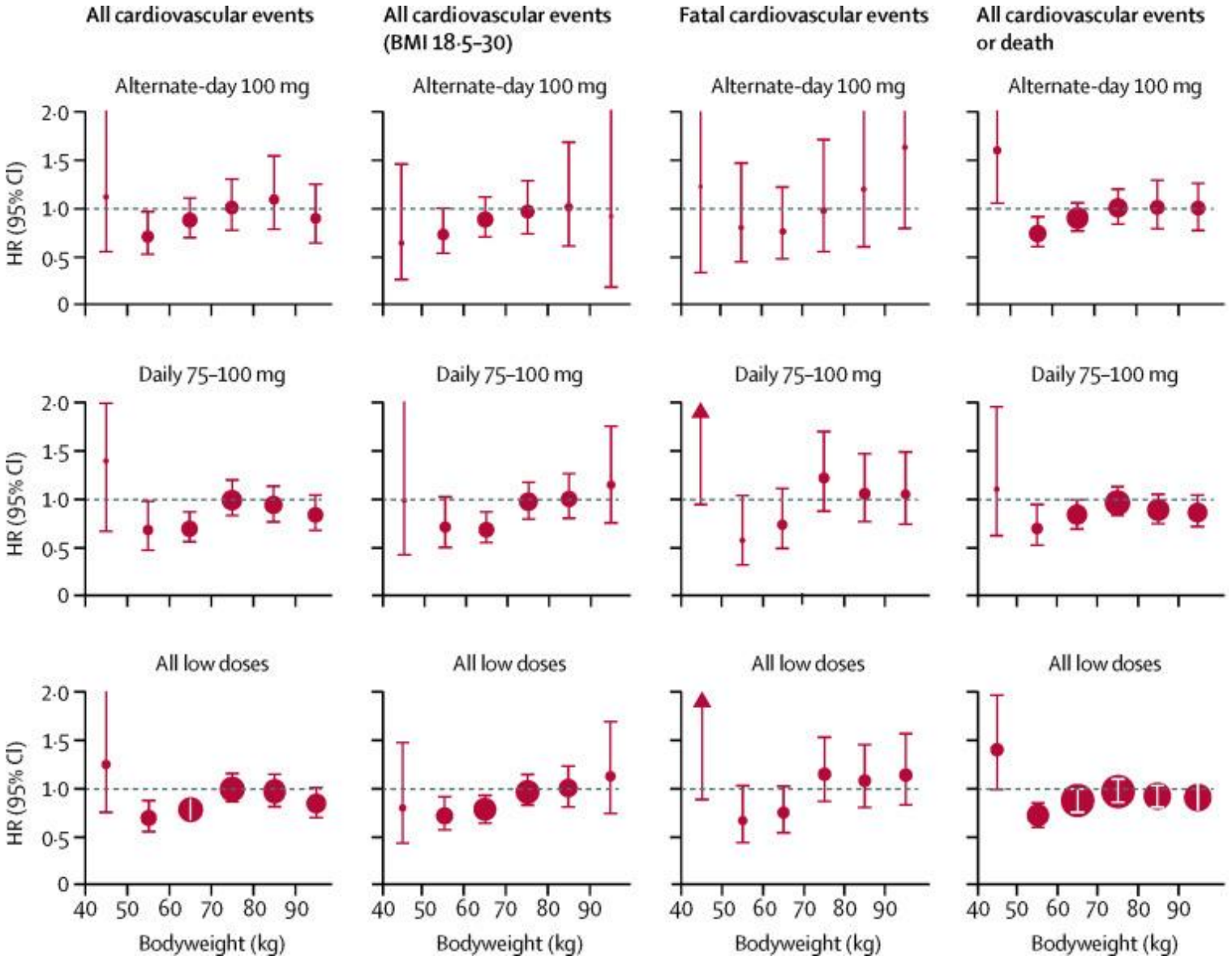
Variable	Proximal		Distal		Rectal	
	OR	95% CI	OR	95% CI	OR	95% CI
Sigmoidoscopy and/or colonoscopy and polyp history						
Sigmoidoscopy and/or colonoscopy in last 10 years, and no history of polyps	1.00		1.00		1.00	
No sigmoidoscopy and/or colonoscopy in last 10 years	1.82	1.32 to 2.51	3.44	2.31 to 5.11	2.99	1.91 to 4.69
Sigmoidoscopy and/or colonoscopy in last 10 years and history of polyps	2.62	1.52 to 4.50	4.35	2.35 to 8.03	3.19	1.41 to 7.25
Sigmoidoscopy and/or colonoscopy and polyps unknown	0.61	0.17 to 1.04	3.17	1.09 to 4.02	0.37	0.04 to 3.14
No. of relatives with CRC						
0	1.00		1.00		1.00	
1	1.51	1.11 to 2.03	1.45	1.04 to 2.00	1.53	0.92 to 2.55
≥ 2	2.27	1.25 to 4.14	2.09	1.09 to 4.02		
Current vigorous leisure exercise, h/wk						
0	1.00				1.00	
> 0 and ≤ 2	0.86	0.75 to 1.00			0.69	0.48 to 1.00
> 2 and ≤ 4	0.75	0.56 to 1.00			0.79	0.45 to 1.37
> 4	0.65	0.52 to 0.99			0.63	0.36 to 1.10
Aspirin/NSAID use						
Nonuser	1.00		1.00		1.00	
Regular user	0.63	0.49 to 0.81	0.70	0.53 to 0.91	0.70	0.50 to 0.97
Vegetable intake, servings/d						
< 5	1.00					
≥ 5	0.72	0.51 to 1.02				
BMI, kg/m^2						
≤ 29.9			1.00		1.00	
≥ 30			1.08	0.75 to 1.54	1.40	0.95 to 2.06
Age, years						
≤ 65			1.00			
> 65			0.55	0.41 to 0.74		
Estrogen status within the last 2 years						
Negative	1.00		1.00		1.00	
Positive	0.68	0.52 to 0.90	0.48	0.33 to 0.68	0.67	0.48 to 0.94
BMI-estrogen interaction			2.68	1.39 to 5.20		

Freedman *et al*, JCO 2009

Future directions

- Precision prevention
  - Sex
  - Risk assessment
    - Improved ASCVD risk assessment
    - Baseline CRC risk assessment
    - Risk assessment for serious bleeding
  - Dosing by weight

Emerging new findings: Weight and dosing



Rothwell PM et al, Lancet. 2018

Future directions

- Precision prevention
  - Sex
  - Risk assessment
    - Improved ASCVD risk assessment
    - Baseline CRC risk assessment
    - Risk assessment for serious bleeding
  - Dosing by weight
  - Prediction of response
- Shared decision making
- Integrated approaches for both CVD and CRC prevention

Conclusions

- AHA/ACC 2019
  - "Aspirin should be used infrequently in the routine primary prevention of ASCVD because of lack of net benefit"
- Promise in aspirin for CVD and CRC primary prevention, and potential in reducing metastasis among cancer patients
- Need for more precise risk prediction tools and precision based primary prevention guidelines
- Need for shared decision making that take into account patient preferences

Thank you!

Interactions

- Other medications and herbal supplements also may increase your risk of bleeding. Medications that can interact with aspirin include:
- Heparin
- Ibuprofen (Advil, Motrin IB, others), when taken regularly
- Corticosteroids
- Clopidogrel (Plavix)
- Some antidepressants (clomipramine, paroxetine, others)
- Taking some dietary supplements can also increase your bleeding risk. These include:
- Bilberry
- Capsaicin
- Cat's claw
- Danshen
- Evening primrose oil
- Ginkgo
- Kava
- Ma-Huang
- Omega-3 fatty acids (fish oil)